

# INVESTIGATING THE AVAILABILITY OF ANTIMICROBIALS AT KAMUZU CENTRAL HOSPITAL IN MALAWI

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## DECLARATION OF ORIGINAL WORK

I, Miss Tadala Hamisi declare as follows:

1. That the work in this thesis has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.
2. That my contribution to the project was as follows:  
I was the main author of the project proposal for this thesis, as well as the main author for the thesis. I was as the sole data collector and I also conducted data analysis and results presentation. I was also the main author of the publication for the African Health Sciences Journal.
3. That the contribution of others to the project was as follows:
  - a. Professor Fatima Suleman was the main supervisor and spearheaded the direction of the project as well as editing the project proposal and thesis. She was also the link during the submission and acceptance of the project proposal to the Humanities and Social Sciences Research Ethics Committee, Westville Campus. She also assisted with the manuscript editing.
  - b. Professor Lars Smaabrekke as a supervisor assisted in giving direction of the project as well as editing the project proposal and thesis. He also assisted in data analysis and interpretation of the results. He also assisted with the manuscript editing.
  - c. Mr Felix Khuluza as the local supervisor assisted in meeting standards for the proposal to be accepted by the College of Medicine Research and Ethics Committee. He also assisted with the manuscript editing.

4) Signed \_\_\_\_\_ Date \_\_\_\_\_

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## **List of Acronyms**

ABS	Antibiotic Stewardship
ACT	Artemisin based Combination Therapy
AIDS	Acquired Immune Deficiency Syndrome
AMR	Antimicrobial Resistance
ARI	Acute Respiratory Infections
ART	Antiretroviral Therapy
ARV	Antiretroviral medicine
CDC	Centre for Diseases Control and Prevention
CEO	Chief Executive Officer
GDP	Gross Domestic Product
CHW	Community Health Care Worker
CMS	Central Medical Stores
CMST	Central Medical Stores Trust
CoM	College of Medicine
COMREC	College of Medicine Research and Ethics Committee
cStock	Rapid SMS open-source, web-accessible logistics management information system
DALYs	Disability Adjusted Life Years
DHO	District Health Office
DMO	District Medical Officer
EMS	Essential Medicines and Supplies
GoM	Government of Malawi
HAI	Health Action International

HIV	Human Immunodeficiency Virus
HD	Hospital Director
KCH	Kamuzu Central Hospital
LA	Lumefantrine-Artemether
MEML	Malawi Essential Medicines List
mHealth	Mobile Health (technology)
MHSSP	Malawi Health Sector Strategic Plan
MoH	Ministry of Health
MDR-TB	Multi Drug-Resistant Tuberculosis
NCD	Non-Communicable Disease
NMCP	National Malaria Control Programme
NORHED	Norwegian Programme for Capacity Development in Higher Education and Research Development grant
OTC	Over the Counter
QECH	Queen Elizabeth Central Hospital
SC4CCM	Supply Chain for Community Case Management
STD	Sexually Transmitted Diseases
TB	Tuberculosis
TOC	Theory of Change
UKZN	University of KwaZulu-Natal
WHO	World Health Organisation
YLD	Years Lost Due to Disability
YLL	Years of Life Lost

## ABSTRACT

### **Background**

Stock-outs of medicines in Malawian public hospitals affect the majority of the population, and may have serious public health consequences.

### **Aim**

The aim of this study was to identify stock-outs of selected antimicrobials in the years 2014 and 2015 at Kamuzu Central Hospital (KCH), and investigate whether there were alternative treatments available.

### **Methods**

This was a retrospective, cross-sectional observational study. The sample list of 70 medicines represented antimicrobial agents on the Malawi Essential List of Medicines. Data was collected from Pharmacy stock-keeping records and analysed in Microsoft Excel. The following calculations were made; total number of days out of stock per year, total number of episodes out of stock and stock-out duration.

### **Results**

The most available group were antituberculosis at stock-out median number of days of 10 and 62, in 2014 and 2015 respectively. Most stocked-out was the antiretroviral medicines group with a median stock-out days of 175 and 170 in 2014 and 2015 respectively. Antibiotic agents had median number of days of 65 and 96. Specifically penicillins had median stock-out days of 86 in 2014 and 119 in 2015 whereas cephalosporins had 67 in 2014 and 80 in 2015. Macrolides had 36 and 87 median stock-out days in 2014 and 2015. Antimalarial medicines had median number of stock-out days of 55 in 2014 and 32 in 2015. Alternative first line treatments for malaria and TB were available; however, HIV, STD and pneumonia alternatives were not always available.

### **Recommendations**

Stock-outs of antimicrobials occurred at KCH in both 2014 and 2015. In some cases, alternative therapy was unavailable, and patients probably received inadequate treatment. This negatively affects patient outcome in addition to the possible negative public health effects due to development of antimicrobial resistance.

# **CHAPTER I: INTRODUCTION**

## I INTRODUCTION

### 1.1 Background of Malawi

Malawi is a landlocked Sub-Saharan country with a total area of 118,484 km<sup>2</sup>, and there are 13 districts in the Southern Region, nine in the Central Region and six in the Northern Region. Each district is subdivided into Traditional Authorities and these are governed by Chiefs (1). Currently, the life expectancy in Malawi is 62 years for women and 58 years for men, which is an increase from the 55 years for both men and women that was projected in 2010 (1,2).

Data from 2015 showed that the current population is at 17,000,000, estimated to reach 19.1 million in 2020, and 45% of the population is below the age of 15 years (2,3). Approximately 15% of the Malawi population is urban, with the rest living in the rural areas (1,4). The agricultural sector accounts for 35% of Gross Domestic Product (GDP), and supports more than 85% of the population (1,2). As of 2009, 39% of the country population was living below the poverty line(5).

Data from 2016 showed that Malawi is the poorest country in the world, with a GDP per capita of US\$255 (6). According to the Malawi Health Sector Strategic Plan (HSSP) 2011-2016 version, 'the sources of revenue for funding public services are taxes on personal income and company profits, trade taxes and grants from donors' (5). The health sector was third on the list of recurrent expenditures at 12.4% in the fiscal year of 2010/2011 (5). As per the Abuja Declaration of 2001, the target expenditure for the health sector should be at a minimum of 15% of total government expenditure (5). Public hospitals in Malawi are funded through Ministry of Health (MoH) and provide free health care to all Malawians. The control of the funding is centralised to the MoH (7).

### 1.2 Health Indicators in Malawi

The Global reference list of Health Indicators, published by World Health Organization (WHO) in 2015, includes 100 health indicators. The aim of the reference list is to '...promote greater alignment with and investment in one country-led health sector platform for results and accountability that forms the basis of global reporting' (8). These have the following subsections: Health status indicators; Risk factor indicators; Service coverage indicators and; Health systems indicators. Of note, under health systems indicator there is 'availability of essential medicines and commodities' indicator (8). The National health indicators are in draft form as of September 2015. The draft includes 22 sections of indicators, some of which are not in the Global reference list, nor in the Malawi Health Sector Strategic Plan (MHSSP) 2011-2015 version. The MHSSP includes 38 core indicators that have baseline measurements from 2010 with targets for 2016. Indicator number 29 illustrated that 85% of monthly drug deliveries were witnessed by health facility committees, with a target of 95% in 2016. Indicator number 30 has a tracer list of drugs that includes

antibiotics like cotrimoxazole, gentamicin, metronidazole and benzyl penicillin. This indicator is aimed to measure the percentage of health facilities experiencing stock outs of the tracer drugs, and the target for 2016 is to ensure that there is 100% availability of these drugs at all health facilities (5). These 38 core indicators plus other important health public health interventions form the Essential Health Package (EHP) (5).

A baseline assessment in 2010 revealed that the EHP Coverage was at 74%, and the population satisfaction with health services was 83.6% and 76.4% for urban and rural areas respectively. It has been reported that the ‘prevalence of diseases such as malaria, Acute Respiratory Infections (ARI) and diarrhoea is higher among the poor people than those who are rich’ (5). In other words, the prevalence of these diseases is inversely associated with socio-economic factors. This suggests that a reduction in poverty would assist in the successful implementation of the EHP. A study conducted by Mueller et al concluded that the two major constraints that hindered the successful implementation of the EHP were: staff shortages caused by vacancies and frequent/unplanned training sessions and meetings and; shortages of vital medicines, although it was noted that the shortages were more pronounced in health centres than in public hospitals (9). It was stated that although decentralisation of procurement of medicines had been introduced in 2006, implementation of the procurement process was not complete at the time of the study in 2010. The survey highlighted that some priority areas of the EHP are adverse neonatal and maternal outcomes, common injuries and communicable diseases like tuberculosis (TB) and Human Immunodeficiency Virus Acquired Immunodeficiency Syndrome (HIV/AIDS).

### **1.3 The burden of disease in Malawi**

A study from 2009 indicated that the most common causes of death in Malawi were communicable diseases (at just under 80%), and this proportion was higher than other Sub-Saharan countries (10). ‘Communicable disease means an illness caused by an infectious agent or its toxins that occur through the direct or indirect transmission of the infectious agent or its products from an infected individual or via an animal, vector, or the inanimate environment to a susceptible animal or human host’ (11). The major communicable diseases in Malawi are; malaria, lower respiratory tract infections, diarrhoeal diseases, TB and HIV/AIDS (5). Approximately 34% of yearly out-patient visits are due to malaria, and malaria is also reported to cause 40% of all hospital deaths. About 40% of children under 5 are hospitalised due to malaria. It is also estimated that 10.6% of the Malawi population aged 15-49 years is living with HIV, with 55 000 incident cases every year. Although there has been 50% decline in the prevalence of TB from 1995-2010, TB still causes approximately 3% of all deaths in Malawi (2,11,12).

Figure 1 below gives a more detailed picture of the top ten diseases and risk factors in Malawi (5). According to the list, HIV/AIDS was the highest cause of death, at 33.6%. This was followed by lower respiratory infections and then malaria. Cerebrovascular diseases were higher than tuberculosis which was at 2.4%. On the same note, due to the reported rise of non-communicable diseases, the ministry opened a Non-Communicable Disease (NCD) Department at Headquarters (5). A survey that was conducted in 2009 indicated that hypertension was the most prevalent NCD at 32.9%, with cardiovascular diseases and diabetes at 8.9% and 5.6% respectively (5).

Top 10 risk factors			Top 10 diseases/injuries		
Rank	Risk factor	% of total	Rank	Disease	% of deaths
1	Unsafe sex	34.1	1	HIV/AIDS	33.6
2	Childhood and maternal underweight	16.5	2	Lower Respiratory Infections	11.3
3	Unsafe water, sanitation and hygiene	6.7	3	Malaria	7.8
4	Zinc deficiency	4.9	4	Diarrhoeal diseases	7.6
5	Vitamin A deficiency	4.8	5	Conditions arising from perinatal conditions	3.2
6	Indoor smoke from solid fuels	4.8	6	Cerebrovascular disease	2.8
7	High blood pressure	3.5	7	Ischaemic heart disease	2.6
8	Alcohol	2.0	8	Tuberculosis	2.4
9	Tobacco	1.5	9	RTA	1.3
10	Iron deficiency	1.3	10	Protein energy malnutrition	1.0

*Figure 1 Top Ten Diseases and Injuries in Malawi. Source: Malawi Health Sector Strategic Plan (Ministry of Health 2011)*

The most common intervention for treatable conditions is medical treatment. As such, one of the priority areas in the MHSSP is ‘to ensure the availability of adequate quantities of high quality safe and affordable Essential Medicines and Supplies (EMS) for effective delivery of the EHP to all Malawians’ (5). The Central Medical Stores Trust (CMST) is responsible for supply of medicines in all public health facilities, and this entity plays a key role in delivery of the EHP.

#### **1.4 Procurement of Medicines at CMST**

CMST was implemented in 2010 ‘to ensure continuous, uninterrupted and adequate supply of approved, quality and affordable medicines and medical supplies to public health facilities’ (13). CMST branches are the Mzuzu Northern Region Branch, the Lilongwe Central Region Branch and the Blantyre Southern Region Branch (14,15). CMST Headquarters is based in Lilongwe, and in addition to the Director of Corporate Services, the team comprises seven members; the Procurement Manager, two senior officers and four procurement officers (16). The Headquarters dispatches medicines to the three branches (13,17), and the Lilongwe Branch supplies drugs to KCH, as well as the eight other districts in the Central Region. It is not clear whether the recent interrupted supply of medicines in public hospitals in Malawi can and should

be solely linked to CMST, or the hospitals not being able to adequately quantify or order medicines on time, or the centralised procurement system in general.

In the 2014/2015 zero aid budget of K743 billion, the MoH was allocated K65 billion (approximately 8%) (18). This was therefore the full amount that all public hospitals were able to use in order to procure medicines from CMST. This is against a baseline survey of the MoH 2010-2011 of 12% of the total budget, with a target of at least 15% (5). The Minister of Finance, Economic Planning and Development acknowledged that this figure was too low for MoH, and he was quoted to have ‘acknowledged the deficit but banked his hopes on donors who bankroll most projects in the sector’(18). However, despite the country previously relying on donor funds, Malawi had to implement the Zero aid budget in 2013 as a result of donors freezing aid to the country due to the on-going ‘cash gate’ scandal investigations (19). The MoH and public hospitals, now predominantly funded by Government, had to utilise the few funds provided by the zero aid budget. The effects of implementation of the budget at KCH are yet to be published.

### **1.5 Kamuzu Central Hospital (KCH)**

KCH is a 1200 bed Public Hospital located in Lilongwe (20). KCH caters for the approximately 6 million Malawian population based in the central region (1). KCH offers tertiary health care service and is a teaching hospital. The out-patients department treats an average of 10 000 patients in a month (21,22). The vision of the hospital is ‘To be an accredited centre of excellence for tertiary health care services for people living in Malawi’(20). As a referral hospital, KCH also supports surrounding district hospitals with patient care as well as improving their provision of quality care (20).

The National Medicines Policy June 2015 version highlights the problems that public hospitals are facing, including shortages of essential medicines which have been attributed to the failure to deliver the EHP (23). It further outlines some of the causes of the drug shortages as: weak logistical information systems; lengthy procurement processes and; poor quantification and specifications. Additionally, it listed other problems in the health system; limited financial and human resources; increased demand for quality health by the growing population; a fragile pharmaceutical industry and; pilferage of medicine. This information further supports the media reports of the medicine shortages in the public hospitals (24,25).

### **1.6 Antimicrobial Resistance**

Amidst reports on the medicine shortages in the country, there has been a growing spread of Antimicrobial Resistance (AMR) in the continent and worldwide (12,26,27). AMR has been defined by WHO as ‘resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it’ (12). The overall goal of the global action plan on AMR ‘is to ensure for as long



as possible, **continuity** of the ability to **treat and prevent infectious diseases with effective and safe medicines** that are quality assured, used in a responsible way, and accessible to all who need them.

Malawi has seen a rise in Multi Drug-Resistant Tuberculosis (MDR-TB) cases in recent years. MDR-TB is resistance to at least Isoniazid and Rifampicin (28). Although the MDR-TB prevalence in Malawi is low, at 4.8% among retreatment cases, and 0.4% among new cases, the emergence of the condition is still a disadvantage (29). It is therefore necessary to maintain the continuity of access to antibiotics at all health care levels and promote rational treatment in order to prevent deaths from treatable diseases.

At the WHO World Health Day in 2011, the theme was ‘Antimicrobial Resistance: No action today, no cure tomorrow’(30). Two of the six action points that were discussed in the policy package to combat AMR were:

- Ensure uninterrupted access to essential medicines of assured quality
- Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care

It has been noted that there is failure to promote rational use of medicines if there is interrupted supply and inequitable access to essential medicines. As a result, shortages of antibiotics are one of the reasons of the growing AMR in the world (31).

The indirect impact of AMR, however, extends beyond increased health risks and encompasses economic loss due to reduced productivity caused by sickness of both human beings and animals and higher costs of treatment (27). As such, KCH and Malawi as a country would do well with the successful implementation of Antimicrobial Stewardship and Conservancy Committees and activities. The antibiotic stewardship drivers that were developed by CDC are:

- Availability of expertise at the point of care
- Data monitoring and transparency
- Appropriate selection of treatment, administration and de-escalation
  - Timely antibiotic management, which includes starting treatment promptly and have antibiotics readily available

These objectives would not be achieved if antibiotics are unavailable in hospitals. At the ‘Championing African Action on Antibiotic Resistance: strategies and innovative solutions’ workshop held in April 2014, it was outlined that the three main groups in the category of AMR medicines are (26):

- Antiviral agents – for example those used in the treatment of HIV and Herpes
- Antibiotics including those used to treat TB
- Anti-parasitic agents – for example those used to treat malaria

## **1.7 Antibiotic Stewardship in Malawi**

Currently, there is no documented evidence of Antibiotic Stewardship Program at KCH, nor the public hospitals in Malawi. This study can help to reveal whether there were any medicine stock-outs of antimicrobial medicines in the years 2014 and 2015. Additionally, this study could assist in investigating if alternative treatment for important communicable diseases were available, if the first line treatments were indeed out of stock. The findings of this study can assist in bringing solutions to alleviate medicine supply problems at KCH.

## **1.8 Research Question and Study Objectives**

### ***Research Question***

Did KCH have stock-outs of selected antimicrobials in the years 2014 and 2015? Were there any alternatives for treatment available when these antimicrobials were out of stock?

### ***Study Aim***

The aim of this study was to identify stock-outs of selected antimicrobials in the years 2014 and 2015 at KCH.

### ***Objectives***

- 1) To identify whether any antimicrobials from the Malawi Essential List 2009 were out of stock at KCH during 2014 and 2015
- 2) To investigate for how long the specific antimicrobials were unavailable
- 3) To evaluate if any alternative antimicrobial treatment were available for a specified list of diseases

The next chapter highlights the literature that is available on this topic. It will analyse the types of studies conducted as well as the methodologies used, and finally, it will summarise the research gaps on this topic.

Chapter III will be a manuscript that will be submitted for publication in a journal accredited by UKZN. This chapter will have the introduction, methodology and results sections. The results will be discussed and a short conclusion will be given. Chapter IV which is the final chapter will present the conclusion for each objective and other significant findings will also be presented here.

## **CHAPTER II: LITERATURE REVIEW**

## II LITERATURE REVIEW

### 2.1 Literature Search Strategy

The literature review will highlight some of the studies that have been conducted concerning topics similar to this study's research question. The sources used were Pubmed, Hinari, Google Scholar, and Google. The search strings that were used in Pubmed were: {Evaluating Drug\* Supply OR Evaluating Medicine\* Supply OR Analysing Drug\* Supply OR Analysing Medicine\* Supply} AND {Central Hospital OR Tertiary Hospital OR Referral Hospital} AND {Kamuzu Central Hospital OR Lilongwe OR Malawi OR Africa OR World OR Global} AND {Central Medical Stores OR Central Medical Stores Trust} AND {Cross Sectional Studies} AND {Drug Stock Out OR Medicine Stock out OR Drug Availability OR Medicine Availability} AND {Communicable diseases OR Malaria OR HIV OR AIDS OR HIV/AIDS}.

The inclusion criteria for the papers identified were:

- Studies that outline Medicines Supply Chain Systems
- Studies that reference the need for constant supply of the essential Medicines
- Studies that reference medicines supply to Public Hospitals in Malawi
- Studies and articles that reference stock-out of medicines in public hospitals
- Studies and documentation of communicable diseases in Malawi.
- Studies, reports and documentation that refer to AMR and ABS

The exclusion criteria were:

- Studies that are not written in English
- Studies that were published before 2007

The summary of the final included articles are presented according to headings listed below.

### 2.2 Studies on Availability, Affordability and Access to Essential Medicines

WHO describes essential medicines as those that are 'most efficacious, safe and cost effective for priority conditions' (49). Antimicrobial agents are considered essential, and they appear on the Malawi Essential Medicines List (MEML). Quite a few studies have been conducted locally and internationally on essential medicines, most of which evaluate access, use, supply and availability of the medicines in hospitals (35,36,46,50). Many studies have used the WHO-HAI (Health Action International) methodology for

assessing the availability, access and affordability of medicines for country-wide studies (50–53). The WHO-HAI methodology is validated and has been considered a standard for studies on drug availability and access (54). It allows for easier comparison as the methodology provides a standardised list of medicines which has:

- A global list of 14 medicines that is supposed to be included in all international studies
- A regional list of 16 medicines that differs from region to region but allows for comparison across countries in the same region
- A supplementary list of a minimum of 20 medicines that are selected at country level for their local importance

In their systematic analysis, Bazargani et al aimed to prove that essential medicines are more available than non-essential medicines and although the results supported this hypothesis, there was generally a reverse trend of national income level and the availability of essential medicines. However, in this study, comparison of availability was not identical as the country list drugs ranged from a total number of 17 in Yemen and 185 in India. This therefore led to difficulties in terms of general comparison of availability. The study also did not include enough countries per WHO region allowing the authors to compare and generalise the results. Finally, the studies are cross-sectional which give results of a point in time, and may not give a true picture of the general situation due to lack of longitudinal data.

Most of the studies conducted are of a cross-sectional mixed methods nature, and the advantage is that they can extrapolate conclusions from both key stakeholders' opinions as well as combine results with the quantitative data collected (9,34,35,55,56). As Wagenaar et al in their Mozambique study on stock-out of essential health products said; 'data collection was conducted at one point in the year (July-August) and therefore may not be representative of EHP availability year round' (35).

A case study undertaken in Malawi was reported to have been conducted in 6 districts for a period of three years (57). However, the data presented focused on only one of the 28 districts in the country, and the community were used as sources of information on drug stock-outs. The authors stated that this information was used to push for policy change at higher levels, but the exact policy changes were not specified. There was an interview conducted with the District Health Officer (DHO) from the district that the study was undertaken. Data from a single person as well as a single district could be biased, and are hardly representative for the whole country. Additionally, the communities were indeed empowered to tip of the study investigators on drug stock-outs via messages sent to a central number, but there was no mention of evidence to support these reports.

A report from the Eastern Cape Mthata Depot in South Africa estimated the drug theft at ZAR 220 000 in the month of May 2011 (58). The report also mentioned other factors that led to drug shortages in health facilities supplied by the depot, ranging from national stock-outs possibly caused by supplier capacity challenges, to staff shortages at the depot and health facilities. Key informant interviews gave other reasons of drug shortages caused by poor supply chain management and a lack of software to accurately and efficiently manage stock for patients on HIV treatment. However, there was no data presented to support these reports of stock-outs from the affected clinics. The report focused on stock-outs at the beginning of the pipeline, but did not collect data from the end user units themselves. This created a gap in the data in the report.

Similarly, in their cross-sectional study on ‘stock-outs of anti-retroviral drugs and coping strategies used to prevent treatment change’ by Mori and Owenya, the main data collection tool was semi-structured interviews (34). The advantage in their study was that they interviewed two staff members in each of the 20 facilities selected, although this information was not verified by collecting quantitative data from the clinics. To add on to this, the authors used purposive sampling to select the clinics included in the study. Considering that the sample sites were HIV clinics, this was the most cost-effective and fastest way to conduct the study. The disadvantage of the study was that the clinics that borrowed drugs from other clinics or referred patients to those clinics would recommend clinics in similar situations to the study data collectors. As such, it is hard to generalise the data collected in the study.

Most studies published tend to focus on specific communicable diseases, especially malaria (42,44,59,60). The aim of these studies varies from assessing the availability and accessibility of the antimalarial medicines, to testing the quality of the medicine on the market. The main area of interest appears to be studies that investigate stock-outs of antimalarial medicines in hospitals and health centres (37,40,48). During the 33-month data collection period, the authors found that 6.5% of ACTs in all private pharmacies sampled were Government property. The samples were collected during three periods of two months each. It was unfortunate that there was no data collection conducted in nearby public facilities to check for possible stock-outs of the same samples, and to calculate the magnitude of the stock-outs in the public facilities. Secondly, the samples could have been collected at least monthly or quarterly in order to give a clearer picture of the magnitude of the problem.

### **2.3 Consequences of Stock-outs of Essential Medicines**

Stock-out of medicine is defined as ‘having less stock of a medicine available in a public health facility than required for patients as stipulated by national guidelines’ (32). There are many serious consequences that occur due to stock-outs of antibiotics and essential medicines, other than the growing problem of AMR

(12,27,33). A few studies have been conducted on this topic, both locally and internationally (34–37). They focus on specialised care, and outline the consequences for interruption in treatment, patients' costs, increased risk of drug resistance and increased risk of death (34,36,37). Other studies look at a more holistic approach, and at medicines stock out as being one of the factors of the failure to provide adequate services to patients (9).

Mueller et al (2011) stated that the EHP focuses on the local burden of disease in Malawi, and that one of the major constraints to its successful implementation was 'shortages of vital drugs at all levels of facilities' (9). Priority interventions targeted in the EHP include TB and HIV/AIDS, as well as adverse neonatal and maternal outcomes. Essential medicines were available to treat sufficient number of patients in only 27% of health centres (9). On the other hand, sulfadoxine/pyrimethamine, used for malaria treatment at the time of the study, was available in only 42% of the health centres. The study did not detail the actual consequences of these medicines shortages.

A report that was released by Uganda Ministry of Finance in 2015 outlined the implications of stock-outs of medicines at health facilities in the public sector (32). The results showed that there were stock-outs in 43-79% of the sampled health facilities. The report concluded that the implications of the stock-outs were higher death rates due to malaria and cancer; patients were burdened with increased costs as they had to buy medicines from private pharmacies; some children had incomplete immunization due to stock-outs of vaccines and; in some cases there was rationing of medicines which resulted in patients being given only half the prescribed dosages.

### ***2.2.1 Consequences of Stock-outs of Anti-retroviral Medicines***

Malaria and HIV/AIDS are amongst the top three causes of death in Malawi and an adequate supply of medicines is vital in managing the conditions and improving the disease outcomes. Rationing of medicines was reported in Tanzania in a cross-sectional study that was conducted by Mori and Owenya in 2011 (34). Due to shortages of anti-retroviral medicines, patients' refill periods were shortened from a month to two-weeks at times, so that each patient could at least receive some medicine. This increased transportation costs for the patients. In some cases this translated to interrupted ART treatment, and for some patients treatment regimens had to be changed either temporarily or even permanently. As a result, there were fears of emergence of drug-resistant HIV strains which would ultimately lead to rapid disease progression and increased costs in order to treat patients with second line regimens.

A similar study conducted in Cote d'Ivoire in 2010 followed up patients on ART for a period of 24 months (37). The aim of the study was to collate the impact of change in treatment regimens for these patients. There were two primary outcomes namely: ART modification, which involved at least one medicine



substitution, or discontinuation of treatment for at least one month, both due to medicine stock outs. The secondary outcomes were interruption of care or death. During the study, a total of 1554 adults were enrolled, of which 72 patients discontinued treatment and 98 modified their regimen because of medicine stock outs (37). It was reported that stock outs leading to discontinuation of treatment increased the risk of interruption in treatment care or death, but medicine substitutions did not. There were also 26 deaths (3%) during the study period, although some of these were related to other factors.

The secondary factors that result from stock out of ARVs include; increasing the risk of HIV drug-resistant strains; treatment failure; increased risk of death; treatment interruption; increased costs for patients; and increased costs for the health systems (34,35,37–39). However, there is a need for more prospective studies so that the correlation of strengths and factors can be quantified. What most studies have managed to show is that stock outs in ARVs do occur in countries in Africa, and that the consequences are negative and detrimental for the patients.

### ***2.2.2 Consequences of Stock-outs of Anti-malarial Medicines***

On a similar note, studies have highlighted the consequences of stock-outs of short duration in high-risk diseases like malaria. Likewise, other African countries have invested a lot of time and funds in order to prevent stock outs of malaria medicines, as is evidenced by the ‘SMS for life’ project that was piloted and is in use in Tanzania, Uganda and Kenya (40–42). Malaria medicines stock outs have been reported in a lot of countries including Malawi (35,43–46).

In 2007 to 2010, a study was conducted in 11 African cities (including Accra, Nairobi, Kigali, Lagos, Kampala and Dar es Salaam), whereby the investigators were assessing the extent of antimalarial medicines diversion from the public sector to the private sector and to other countries (45). As a result of the diversions, stock-outs were caused in the public sectors. One of the consequences of these man-made stock outs is that donors can lose trust in recipient countries, therefore putting prospects of further funding at risk (43,45). It should be noted that medicines for malaria in most African countries are funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria (43). It has been reported that the Global Fund has suspended grants to countries like Zambia and Uganda in the past, due to mismanagement of medicines and money (45). Consequently, if donors pull out such programs in Malawi it can be detrimental for the country (5).

In their study, Bates et al also found out that due to the man-made stock outs of antimalarial medicines, there was a tendency of public hospitals to alternatively use expired medicines that they had available (45). Another area of concern is the fact that there was an increased trade in counterfeit and sub-standard medicines in the private sector, which resulted in the dispensation of unsafe medicines to patients (45).

A systematic review including six studies was conducted in order to assess clinicians' prescribing practices in the presence as well as in the absence of malaria medicines (47). The studies reported on prescriber practices in relation to Artemisinin Combined Therapy (ACT) stock. The review found that sometimes prescribing guidelines are not adhered to even when stock is available, however, there was some correlation between the availability of ACT and prescribing practices. Of note, generally ACT prescriptions increased when ACT were available, and lessened when ACT were out of stock. The increase in prescribing practices was also associated with in-service trainings as reported in one of the studies from Uganda (47). A study from Kenya however, stated that there was rationing in prescribing policies of ACT during ACT stock outs as it was mentioned that there were 'shortages of different dose packs and erratic supply causing health workers to ration the drug to those deemed to have greatest need or who seem most "deserving" (47). This would explain the decrease in prescribing of ACT when there were low stock levels.

A study conducted in Tanzania in 2013 analysed health care workers practices in the absence of ACT, as well as the expenditures of the patients seeking alternative sources of treatment (48). The data for the study was extracted from the 'SMS for Life' project, and household longitudinal survey data. The cost of treatment for patients included meals, transport fares, consultations fees as well as the cost of medicines. The treatment cost of accessing ACT in the public sector was found to be higher than normal, as health care workers were found to be charging user fees to patients who were eligible for free services (48). The private sector was collectively 19% more expensive than the public sector for patients. In conclusion, it can be presumed that ACT stock outs in the public sector can increase expenditures for patients due to health care workers taking advantage of the situation and charging user fees or charging for the medicines. On the other hand, expenditure also increases for care in the private sector. The study limitation was that the sample size was low, and more reliable data could be gathered if the study was conducted at national level (48).

The consequences of stock outs of antimalarial medicines in the public sector affects the patients who are unable to access treatment, or they may end up buying substandard or counterfeit medicines in the private sector (45,48). Alternatively, prescriber practices are affected by the availability of antimalarial medicines and stock outs could encourage bad prescribing practices (47). On a more national note, man-made stock outs in public hospitals that result from theft or diversion of medicines lowers the opportunity for future funding or grants for the health systems in countries that require donor aid (43,45).

## **2.4 Research Gaps**

It is quite evident that stock outs or shortages of medicines have been found in other African countries, and there is some evidence of the same in Malawi (9,35,38–40). Studies in Africa have substantially investigated stock outs of essential medicines, and most especially on the communicable disease medicines

like malaria and HIV (36,40,44,55,61). There have also been pilot studies on the use of mHealth systems and tools that have proved to be successful in improving the availability of medicines through improved supply and logistic systems, for example ‘SMS for Life’ and cStock in Malawi (40,42,62). However, the external validity of some studies are questionable due to small sample sizes, restricted geographical areas for study sites and at times deficient methodologies. The mHealth tool and cStock have only been piloted at community centre level. It is unclear if the tools can be used in order to improve the availability of medicines in central hospitals (62). There is therefore a need to conduct studies on the use of the tool in central hospitals in Malawi. On the other hand, the ‘SMS for Life’ tool has been piloted on malaria medicines and commodities, but it is yet to be extended in to other health commodities (40,42). Positive strides have been taken to improve the availability of essential medicines through the use of mHealth, however, here is a gap in evidence to support the use of the mHealth solutions in hospitals that service a larger sample of patients.

There have been studies that have highlighted the consequences of medicines stock out or shortages, especially in malaria and HIV (34,37,45). The studies have outlined different angles in terms of consequences of stock outs of the medicines used to treat these conditions, ranging from pharmacoeconomics to the impact on disease progression. However, the authors were unable to directly link the unavailability of HIV medicines and the outcome for patients during the study (37). In Malawi, there seems to be no evidence of studies conducted in order to fully assess the impact or the consequences of shortages of essential medicines. There is a need for prospective studies in order to assess how medicines shortages and stock outs impact the economy of the country, as well as the welfare of the people.

Studies that have been conducted in Malawi usually aim on the supply chain deficiencies (38,39), but studies on how these deficiencies affect the communities and the patients are lacking. There is a need for pooled resources and expertise to conduct such studies or to build onto completed studies. The country relies on media reports when it comes to the medicines supply status of the country (63,64). There is a need for studies to assess if these reports are indeed true, as well as to inform on possible improvement on medicines shortages.

## **CHAPTER III: MANUSCRIPT**

**Title:** Investigating the availability of antimicrobials at Kamuzu Central Hospital in Malawi

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### III MANUSCRIPT

#### **Abstract**

#### ***Background***

Stock-outs of medicines in Malawian public hospitals affect the majority of the population, and may have serious public health consequences.

#### ***Aim***

The aim of this study was to identify stock-outs of selected antimicrobials in the years 2014 and 2015 at Kamuzu Central Hospital (KCH), and investigate whether there were alternative treatments available.

#### ***Methods***

This was a retrospective, cross-sectional observational study. The sample list of 70 medicines represented antimicrobial agents on the Malawi Essential List of Medicines. Data was collected from Pharmacy stock-keeping records and analysed in Microsoft Excel. The following calculations were made; total number of days out of stock per year, total number of episodes out of stock and stock-out duration.

#### ***Results***

The most available group were antituberculosis at stock-out median number of days of 10 and 62, in 2014 and 2015 respectively. Most stocked-out was the antiretroviral medicines group with a median stock-out days of 175 and 170 in 2014 and 2015 respectively. Antibiotic agents had median number of days of 65 and 96. Specifically penicillins had median stock-out days of 86 in 2014 and 119 in 2015 whereas cephalosporins had 67 in 2014 and 80 in 2015. Macrolides had 36 and 87 median stock-out days in 2014 and 2015. Antimalarial medicines had median number of stock-out days of 55 in 2014 and 32 in 2015. Alternative first line treatments for malaria and TB were available; however, HIV, STI and pneumonia alternatives were not always available.

#### ***Conclusions***

Stock-outs of antimicrobials occurred at KCH in both 2014 and 2015. In some cases, alternative therapy was unavailable, and patients probably received inadequate treatment. This negatively affects patient outcome in addition to the possible negative public health effects due to development of antimicrobial resistance.

## Introduction

Availability of essential medicines in hospitals is important for improving patient care. For a successful supply of essential medicines in hospitals, there is a need for all stages of pharmaceutical management framework (selection, procurement, distribution and use) to be implemented (1). However, in majority of low-income countries, various stages of pharmaceutical management framework are disrupted leading to medicine stock-outs (2). This is true for Malawi as well.

Among the key problems facing the pharmaceutical sector in Malawi was shortages of essential medicines (3). Some causes of the medicine shortages were weak logistical information systems, lengthy procurement processes, and poor quantification and specifications. Additional problems in the health system were limited financial and human resources, increased demand for quality health by the growing population, fragile pharmaceutical industry, and medicine pilferage in the supply chain and user facilities. Medicine shortages have attributed to failure to deliver the country's Essential Health Package (EHP). Mueller et al (2011) stated that the EHP focuses on the local burden of disease in Malawi, and that one of the major constraints to its successful implementation was 'shortages of vital drugs at all levels of facilities' (4).

Public hospitals in Malawi are funded through Ministry of Health (MoH) and provide free health care to all Malawians (5). As a result, stock-outs of medicines in Malawian public hospitals affect the majority of the population. There are many serious consequences that occur due to stock-outs of antibiotics and other essential medicines (6–8). Generally, medicines stock-outs are one of the factors that contribute to the failure to provide adequate services to patients (4). Some of the more specific consequences of medicine stock-outs are: interruption in treatment, treatment failure, inability of patients to access treatment, patients buying substandard or counterfeit medicines in the private sector, increase in patients' costs, increased risk of death and increased risk of drug resistance (9–12). There is evidence of a rise in Multi Drug-Resistant Tuberculosis (MDR-TB) cases in recent years in Malawi (13). The MDR-TB prevalence in Malawi is at 4.8% among retreatment cases, and 0.4% among new cases (14).

Although there has been 50% decline in the prevalence of TB from 1995-2010, TB still causes approximately 3% of all deaths in Malawi. It is one of the major communicable diseases in Malawi, in addition to malaria, lower respiratory tract infections, diarrhoeal diseases and HIV/AIDS (15). Approximately 34% of yearly out-patient visits are due to malaria, and malaria is also reported to cause 40% of all hospital deaths. About 40% of children under five are hospitalised due to malaria. It is also estimated that 11% of the Malawi population aged 15-49 years is living with HIV, with 55 000 incident cases every year (16,17,8).

The aim of this study was to identify stock-outs of selected antimicrobials in the years 2014 and 2015 at Kamuzu Central Hospital (KCH), and investigate whether there were alternative treatments available.



## **Methods**

### ***Study Design***

This is a retrospective, cross-sectional observational study. The study period was 2014 and 2015.

### ***Study Setting***

The study took place at KCH, a 1200 bed Public Hospital located in Lilongwe (18). KCH caters for approximately 6 million people based in the central region of Malawi (19). KCH offers tertiary health care service and is a teaching hospital. The hospital treats an average of 10 000 out-patients in a month (20,21).

### ***Selection of Medicines***

This study used the Malawi Essential Medicines List (MEML) of 2009 and current guidelines for treatment of HIV, TB and malaria to compile the list of medicines. The list includes all antimicrobials, as well as medicines used in the treatment of malaria, HIV, Tuberculosis and Pneumonia. Purposive sampling, a non-probability method, was used for the sampling process as the medicines were selected due to the fact that they belonged to the selected groups of medicines of interest during the study period.

### ***Data Collection***

All data for the period of January 2014 to December 2015 was collected during March and April 2016 using the KCH Pharmacy stock keeping records. The records have information about medicines stock levels, day-to-day transactions and receipts from CMST as well as donors. These records were: Stock cards, ART clinic stock cards and registers, and TB medicine registers.

### ***Data Analysis***

Microsoft Excel 2013 version was used as database, and all data analysis was conducted using Excel. The following calculations were made; total number of days out of stock per year (365 days), total number of episodes out of stock and stock-out duration of each medicine grouped into months. Data are summarised in tables, and a selection is presented in Tables 1 to 4. Various graphs illustrate the stock-out durations and episodes for each group of antibiotics.

### ***Number of Days Out of Stock***

Out of stock was defined as a day when the medicine was unavailable in the pharmacy drug store as indicated on the stock card. The number of days out of stock for a medicine was calculated by summarising all days when the medicine was unavailable. This also included the day that the medicine was received from Central Medical Stores Trust (CMST) or from a donor. Finally, days out of stock also included days whereby the medicine was at minimum stock, for example one unit, and was not released as per normal

consumption according to the stock card. It was observed that this was a practice to keep these units for emergency use for staff members only.

### *Episodes of Stock-Out*

Once a medicine was out of stock, this was registered as an episode out of stock. The episode of stock-out ended a day after the medicine was received. This meant that there could be several periods of stock-out during one month. Secondly, each new month counted as a new episode of stock-out as the Pharmacy conducts a count on all products every month. If a medicine was out of stock throughout the year, then that medicine had twelve episodes of stock-out.

### *Number of Days Medicine Available*

This was calculated as follows: 365 (number of days per year) – total number of days a medicine was out of stock in that year. In rare cases whereby there was some missing data for a few days or months, the same procedure above applied. If a medicine had data missing for more than half a year (183 days plus) it was excluded from analysis.

### *Ethics Approval*

The study was approved by University of KwaZulu-Natal Ethics Committee (BREC), reference number HSS/1450/015M. Locally, approval was granted from the College of Medicine Research and Ethics Committee (COMREC) with reference number P.11/15/1842. In addition to this, the KCH Research Committee as well as to the Hospital Director (HD) granted approval for the study to take place at the hospital.

## Results

The study sample was 70 medicines and has been grouped into four therapeutic categories: antibacterial, antiviral and antifungal medicines, antituberculosis medicines, antiretroviral medicines, and antimalarial medicines as indicated in Tables 1-4 below. Table 5 highlights the availability of alternative treatment. Note that ND means No Data and NA means Not Applicable.

	<b>Total Number of days drug out of stock (max 365) 2014</b>	<b>Total Number of days drug out of stock (max 365) 2015</b>	<b>Total Number of Stockout Episodes (max 12) 2014</b>	<b>Total Number of Stockout Episodes (max 12) 2015</b>	<b>Stockout Rate (%) out of 365 days 2014</b>	<b>Stockout Rate (%) out of 365 days 2015</b>
<b>Antibacterial, Antiviral and Antifungal Medicines n = 32</b>						
Acyclovir 200mg tab	0	12	0	2	0	3
Acyclovir 400mg tab	324	365	11	12	89	100
Amoxicillin 250mg caps	74	166	6	12	20	45
Amoxicillin elixirs	0	246	0	10	0	67
Ampicillin 250mg inj	12	10	2	2	3	3
Azithromycin 250mg caps	ND	0	ND	0	ND	0
Azithromycin 500mg caps	0	0	0	0	0	0
Benzathine						
Benzylpenicillin 2.4MU inj	0	0	0	0	0	0
Benzylpenicillin 5MU inj	81	31	7	3	22	8
Cefotaxime 500mg inj	ND	36	ND	2	ND	10
Ceftriaxone 1g inj	30	75	1	6	8	21
Cefuroxime 500mg tab	63	128	3	5	17	35

Cephalexin 250mg caps	107	36	4	2	29	10
Chloramphenicol 1g inj	0	0	0	0	0	0
Chloramphenicol 250mg caps	2	224	2	12	1	61
Chloramphenicol susp	0	214	0	7	0	59
Ciprofloxacin 250mg tab	269	197	10	8	74	54
Clotrimazole 500mg pessary	11	44	1	2	3	12
Co-trimoxazole 480mg tab	0	2	0	1	0	1
Co-trimoxazole 960mg tab	0	127	0	6	0	35
Co-trimoxazole syrup	132	0	5	0	36	0
Doxycycline 100mg tab	23	44	3	6	6	12
Erythromycin 250mg tab	58	134	6	7	16	37
Erythromycin susp	50	127	2	5	14	35
Flucloxacillin 250mg caps	0	102	0	6	0	28
Flucloxacillin 250mg inj	231	177	8	8	63	48
Flucloxacillin elixir	365	217	12	10	100	59
Gentamicin 40mg/ml, 2ml inj	7	80	1	4	2	22
Metronidazole 100ml inj	0	83	0	5	0	23
Metronidazole 200mg tab	112	20	9	3	31	5
Metronidazole susp	0	23	0	1	0	6
Nalidixic Acid 500mg tab	0	0	0	0	0	0

Average	65	96	3	5	18	26
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*Table 1 Antibacterial, Anti-fungal and Antiviral Medicine Stock-out Days and Episodes in 2014 and 2015*

	<b>Total Number of drug of stock (max 365) 2014</b>	<b>Total Number of drug of stock (max 365) 2015</b>	<b>Total Number of Stockout Episodes 2014</b>	<b>Total Number of Stockout Episodes 2015</b>	<b>Stockout Rate (%) out of 365 days) 2014</b>	<b>Stockout Rate (%) out of 365 days) 2015</b>
<b>Antituberculosis Medicines n = 5</b>						
Ethambutol 100mg tab	48	25	2	3	13	7
Isoniazid 100mg tab	0	0	0	0	0	0
RH 60/60mg tab	0	0	0	0	0	0
RHZ 60/30/150mg tab	0	0	0	0	0	0
Streptomycin 1mg inj	1	285	1	11	0	78
Average	10	62	1	3	3	17

*Table 2 Antituberculosis Medicines Stock-out Days and Episodes in 2014 and 2015*

	<b>Total Number of drug of stock (max 365) 2014</b>	<b>Total Number of drug of stock (max 365) 2015</b>	<b>Total Number of Stockout Episodes 2014</b>	<b>Total Number of Stockout Episodes 2015</b>	<b>Stockout Rate (%) out of 365 days) 2014</b>	<b>Stockout Rate (%) out of 365 days) 2015</b>
<b>Antiretroviral Medicines n = 10</b>						
Atazanavir / Ritonavir (ATV/r) 300mg + 100mg tab	83	168	3	8	23	46

Efavirenz (EFV) 600mg tab	213	51	9	2	58	14
Lopinavir + Ritonavir (LPV/r) 200mg + 50mg tab	364	184	1	7	100	50
Nevirapine (NVP) 200mg tab	232	151	12	8	64	41
Stavudine (d4T) + Lamivudine (3TC) (Lamivir S30) 30mg + 150mg tab	361	365	12	12	99	100
Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) 1A 30mg + 150mg + 200mg tab	92	365	3	12	25	100
Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV) (5A) 300mg + 300mg + 600mg tab	0	0	0	0	0	0
Tenofovir (TDF) + Lamivudine (3TC) 300mg + 300mg tab	173	120	8	8	47	33
Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) 2A 300mg + 150mg + 200mg tab	0	0	0	0	0	0
Zidovudine (AZT) + Lamivudine (3TC) 300mg + 150mg tab	227	297	10	11	62	81

Average	175	170	6	7	48	47
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*Table 3 Antiretroviral Medicines Stock-out Days and Episodes in 2014 and 2015*

	<b>Total Number of drug of stock (max 365) 2014</b>	<b>Total Number of drug of stock (max 365) 2015</b>	<b>Total Number of Stockout Episodes 2014</b>	<b>Total Number of Stockout Episodes 2015</b>	<b>Stockout Rate (%) out of 365 days) 2014</b>	<b>Stockout Rate (%) out of 365 days) 2015</b>
<b>Antimalarial Medicines n = 13</b>						
Artemether + Lumefantrine 20mg/120mg tab	0	12	0	3	0	3
Artemether + Lumefantrine 40mg/240mg tab	30	79	2	8	8	22
Artemether + Lumefantrine 60mg/360mg tab	118	66	7	6	32	18
Artemether + Lumefantrine 80mg/480mg tab	102	90	10	11	28	25
Artesunate + Amodiaquine 25mg + 67.5mg tab	0	0	0	0	0	0
Artesunate + Amodiaquine 50mg + 135mg tab	0	0	0	0	0	0
Artesunate + Amodiaquine 100mg + 270mg tab	0	0	0	0	0	0
Artesunate + Amodiaquine 100mg + 270mg tab	100	0	4	0	27	0

Artesunate Bicarbonate 60mg inj	14	0	1	0	4	0
Mefloquine 250mg tab	ND	0	ND	0	ND	0
Quinine dihydrochloride 600mg inj	0	0	0	0	0	0
Quinine sulphate 300mg tab	291	117	11	8	80	32
Sulphadoxine + Pyrimethamine (SP) 250mg tab	0	22	0	1	0	6
Average	55	32	3	3	15	9

Table 4 Antimalarial Medicines Stock-out Days and Episodes in 2014 and 2015

First Line Medicine	Alternative medicine	Number of Days First 1st Line Available in 2014	Total number of days alternative available in 2014	Percentage Alternative Available (%) in 2014	Number of Days First 1st Line Available in 2015	Total number of days alternative available in 2015	Percentage Alternative Available (%) in 2015
<b>1.1 Uncomplicated Malaria</b>							
Artemether + Lumefantrine (6)	Artesunate + Amodiaquine 25mg + 67.5mg	365	365	100	353	365	100
Artemether + Lumefantrine (12)	Artesunate + Amodiaquine 50mg + 135mg	335	365	100	286	365	100
Artemether + Lumefantrine (18)	Artesunate + Amodiaquine 100mg + 270mg	247	31	8	299	365	100



Artemether + Lumefantrine (24)	Artesunate + Amodiaquine 100mg + 270mg (adult)	263	265	73	275	365	100
<b>1.2 Tuberculosis (paediatric)</b>							
RHZ 60mg + 30mg + 150mg + E100	Streptomycin	365	342	94	365	80	22
RH tablet 60mg + 60mg + E100mg	RHZ 60mg + 30mg + 150mg + E100	365	365	100	365	365	100
<b>1.3 Pneumonia (adult)</b>							
Amoxicillin 250mg	Amoxicillin + Clavulanic acid 500mg + 125mg	291	ND	ND	199	ND	ND
	Erythromycin 250mg	291	307	84	199	231	63
	Cefuroxime 500mg	291	118	32	199	25	7
<b>1.3.1 Pneumonia (paediatric)</b>							
Amoxicillin 125mg/5ml	Amoxicillin + Clavulanic acid 500mg + 125mg	365	ND	ND	119	ND	ND
	Erythromycin suspension	365	315	86	119	238	65
	Cefuroxime susp	365	ND	ND	119	ND	ND
<b>1.4 HIV (adult)</b>							
Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV) (5A)	Tenofovir (TDF) + Lamivudine (3TC) + Nevirapine	365	132	36	365	175	48

	Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) 2A	365	365	100	365	365	100
Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) 1A	Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) 2A	273	365	100	0	365	100
	Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV) (5A)	273	365	100	0	365	100
Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) 2A	Zidovudine (AZT) + Lamivudine (3TC) + Efavirenz	365	41	11	365	68	19
	Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV) (5A)	365	365	100	365	365	100
<b>1.5 STI</b>							
<b>1.5.1 Genital Ulcers Disease - Herpes, Syphilis, Chancroid</b>							
Ciprofloxacin 500mg	Ciprofloxacin 250mg	ND	95	26	ND	168	46
Benzathine Penicillin 2.4MU	Erythromycin 250mg	365	307	84	365	231	63
Acyclovir 800mg	Acyclovir 200mg	ND	334	92	ND	353	97
	Acyclovir 400mg	ND	41	11	ND	ND	ND
<b>1.5.2 Urethritis</b>							
Gentamycin 40mg/ml		358	NA	NA	285	NA	NA

Doxycycline 100mg	Erithromycin 250mg	342	307	84	321	231	63
Metronidazole 200mg		222	NA	NA	345	NA	NA
<b>1.5.3 Early Syphilis in Adults</b>							
Benzathine Penicillin 2.4MU		365	NA	NA	365	NA	NA
Doxycycline 100mg	Erithromycin 250mg	342	307	84	321	231	63

*Table 5 Availability of Alternative Treatment in 2014 and 2015*

Data was collected for 55/70 (78%) and for 61/70 (87%) medicines in 2014 and 2015 respectively with the rest not collected due to missing data. Stock-outs were experienced in all four categories, most frequently in the antiretroviral medicines group with a median stock-out days of 175 (48%) and 170 (47%) in 2014 and 2015 respectively. The most available group were antituberculosis (ATC code J04A) at stock-out median number of days of 10 and 62, giving stock-out rates of 3% and 17%. Antibiotic agents had median number of days of 65 and 96, giving stock-out rates of 18% and 26%. Finally, the antimalarial medicines had median number of stock-out days of 55 in 2014 and 32 in 2015, thus a stock-out rate of 15% and 9% respectively. The most stock-out episodes were seen in the antiretroviral group, with an average of 6 in 2014 and 7 in 2015. The antituberculosis had the least average stock-out episodes with one in 2014 and 3 in 2015.

There were medicines which had data missing for both years in the group of antibiotics. These were: Acyclovir 800mg tablet, amoxicillin and clavulanic acid 625mg tablet, amoxicillin and clavulanic acid 125/31.25mg elixir, cloxacillin 250mg capsule, gentamycin 10mg/ml 2ml injection, nitrofurantoin 50mg tablet, nitrofurantoin 25mg/5ml suspension and nystatin 100 000IU pessary. These represented 20% of the 40 medicines in this group and 11% of the total 70 medicines. These were not added to the table, nor considered during analysis. The antimalarial agents halofantrine 100mg/5ml suspension and proguanil 100mg tablet had missing data for both years. Mefloquine 250mg tablet had data available for only 148 days in 2015, and all three were not considered for analysis. Artesunate Bicarbonate 60mg injection had 14 days of missing data in January 2014 and it was added in analysis. The total number of medicines excluded in analysis was therefore 11 out of 70 (16%).

### ***Antiviral and Antibacterial Medicines***

Flucloxacillin elixir 125mg/5ml was the only antibiotic with a stock-out rate of 100% in 2014. The following were available throughout both study years: Azithromycin 500mg capsule, benzathine benzylpenicillin 2.4MU injection, chloramphenicol 1g injection, and nalidixic acid 500mg tablet. On the other hand, amoxicillin 250mg capsule had 12 stock-out episodes in 2015, with 166 days out of stock. This shows that even when supplied every month, it is a very fast moving medicine. The same applied for amoxicillin 125mg/5ml elixir and flucloxacillin 125mg/5ml elixir, chloramphenicol 250mg capsule as well as ciprofloxacin 250mg tablet.

### ***Antituberculosis Medicines***

There were no missing data among the five medicines in the antituberculosis group. Three of these medicines were 100% available in both years. There were frequent stock-outs of streptomycin in 2015. This

was uncharacteristic as the medicine was only one day out of stock in the month of December 2014. The data also showed that the hospital did not receive this medicine from May until the end of the year in 2015.

### ***Antimalarial Medicines***

The antimalarial group had data for 13 medicines. Lumefantrine/Artemether (LA) had some stock-outs, with LA 60mg/360mg as the most frequent at 32% in 2014, with 7 stock-out episodes. The paediatric formulation (20mg/120mg) was 100% available in 2014 and had a stock-out rate of 3% in 2015, with 3 stock-out episodes. The highest numbers of stock-out episodes were seen with the adult formulation, at 11 episodes in 2015. Like LA, the second line medicines Artesunate/Amodiaquine (ASAQ) has four strengths representing four age bands and three out of four of the age bands showed 0% stock-out rate in both years, but the adult formulations was stocked-out 27% of the time in 2014, with 4 stock-out episodes from January to April. However, the medicine was not received in the first four months of the year and never went out of stock again once it was received in April. Quinine 300mg tablets, which is prescribed for malaria in pregnancy, was out of stock 80% in 2014 with 11 stock-out episodes, but was more available in 2015 at a stock-out rate of 32%, although it had 8 stock-out episodes. There was 100% availability of quinine injection throughout the study period. Artesunate injection for severe malaria was introduced at KCH midway during January 2014 and no stock-outs were experienced since.

### ***Availability of Alternative Treatments***

Table 5 illustrates what alternative treatment was available for HIV, malaria, pneumonia, as well urethritis, genital ulcers and syphilis. For uncomplicated malaria, there were stock-outs for the first line (LA) in both years except for paediatric formulation in 2014. In 2015 there was 100% availability of the alternative treatment (ASAQ). There was 100% availability of the first two age bands of alternative treatment in 2014, with an extreme low of 8% for the third age band.

First line TB treatment was available in both years and so was the second line tablet formulation. However, the second line streptomycin injection had 94% availability in 2014 and 22% availability in 2015.

The first line paediatric pneumonia treatment, amoxicillin syrup, was available 100% of the time in 2014 and 33% in 2015. There was no data available for alternatives cefuroxime as well as amoxicillin and clavulanic acid suspensions in both years. The other alternative, erythromycin suspension was 86% available in 2014 and 65% in 2015. From March to June, erythromycin suspension was available when amoxicillin syrup wasn't. July, August and October to December both medicines were stocked out at the same times. First line adult pneumonia treatment (amoxicillin 250mg) was 80% available in 2014 and 55% in 2015. There was also no data available for alternative amoxicillin and clavulanic acid tablets. Cefuroxime

tablets had 32% availability in 2014 and 7% in 2015. Erythromycin had higher availability with 86% in 2014 and 63% in 2015.

At the time of study, the first line medicines for herpes and chancroid were acyclovir 800mg, ciprofloxacin 500mg, and benzathine penicillin 2.4MU. There was no data for the first two in both years but benzathine injection was available 100% of the time in both years. The alternative of ciprofloxacin 500mg was ciprofloxacin 250mg and it had 26% availability in 2014 versus 46% in 2015. Acyclovir 200mg was the most available at 92% in 2014 and 97% in 2015. Acyclovir 400mg had 11% availability in 2014, with no data available in 2015. The final alternative, erythromycin 250mg had 84% and 63% availability in 2014 and 2015 respectively. It was also the alternative treatment for syphilis and urethritis. The first line for urethritis, gentamycin injection and metronidazole 200mg, had availability of 98% and 78%, plus 61% and 95% respectively. Doxycycline 100mg was available 94% of the time in 2014 and 88% in 2015. Doxycycline was also first line for syphilis, together with benzathine penicillin.

During the study period, nitrofurantoin was the alternative medicine used to treat acute uncomplicated urinary tract infections in women, with ciprofloxacin being the first line (22). There was no data available for nitrofurantoin, and ciprofloxacin had a 74% and 54% stock-out rate in 2014 and 2015. However, cotrimoxazole an alternative had no stock-outs in 2014 and had 99% availability in 2015.

Data for the 11 medicines the hospital used to treat adult HIV patients were complete except for one product for both years. First line adult HIV treatment had 100% availability for two combinations and 75% for one in 2014. The same applied in 2015 except there was no availability for the third formulation. The tenofovir based first line (tenofovir 300mg and lamivudine 300mg), has two alternatives which were 36% and 100% available in 2014, and 48% and 100% available in 2015. Zidovudine and lamivudine and nevirapine plus tenofovir and lamivudine and efavirenz the two alternatives for first line medicine stavudine 30mg and lamivudine 150mg had 100% availability in both years versus 75% availability of the first line. The alternative treatments for zidovudine and lamivudine and nevirapine were 11% and 100% available in 2014, and 19% and 100% available in 2015.

## Discussion

The prevalence of Antimicrobial Resistance (AMR) in the continent and worldwide has been growing (8,25,7). The overall goal of the global action plan on AMR 'is to ensure for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality assured, used in a responsible way, and accessible to all who need them' (7). Although TB medicines had higher availability of 90%, ARVs were not always available and this was partially explained due to the reason of change of regimens. Considering that HIV/AIDS causes the highest number of deaths (fig 1), the results showed that there is still room for improvement for the medicines to be available in order to combat the high burden diseases whilst preventing the progress of AMR in Malawi.

### *Antiviral and Antibacterial Medicines*

#### *Antiviral Medicines*

It should be noted that some STI medicines including those used in the treatment of syphilis are also supplemented by the HIV program, alongside ARV's which are supplied exclusively by the program. These are acyclovir, fluconazole, clotrimazole, cotrimoxazole, metronidazole and erythromycin. Therefore the availability of these medicines should not be directly linked with the main supply chain system (27). This is significant information as the main supply chain system for public hospitals in Malawi is through the CMST therefore the performance of the main supply chain system should not be portrayed by the availability (or lack of) the parallel supply chain medicines. Other medicines that are supplied exclusively by programs are malaria first line and alternative medicines, as well as TB medicines (3,28). These use parallel supply medicines like the ARVs.

Syphilis is the second cause of deaths after HIV for STI's in Malawi (15), and the first line treatment (benzathine penicillin and doxyxyclyline) was available at a range of 98-61%. Acyclovir is usually prescribed for herpes simplex at a dose of 200-400mg for 5-7 days and for herpes zoster at 800mg five times a day (26), it can be assumed that patients were still treated for both conditions with the available 200mg tablet. The disadvantage being that those on herpes zoster treatment may have to take a higher pill count at a time.

#### *Antibacterial Medicines*

For the treatment of pneumonia in paediatric patients, with the first line amoxicillin being available in 2014 and the alternative substituting for availability in 2015, the large scale of patients were mostly covered. Pneumonia is causing 5.7% deaths in paediatric patients (15).

### ***Antituberculosis Medicines***

TB medicines had an average of 90% availability over the study period. The high availability of TB medicines may contribute to the treatment success rate of 86% in Malawi, which is above the WHO target of 85% (15). Neighbouring country Tanzania has recorded 88% treatment success rate although TB ranks 6<sup>th</sup> on disease burden in the country (23). It should be noted that the success rate for treatment of TB is indirectly linked to the success rate of management and prevention of HIV, as the two diseases are linked with 55% TB cases being found in HIV patients (24). Unavailability of TB medicines to 10% of the target population in the central region could cause spread of TB in the community for those untreated. Additionally, it could cause treatment failure and increased resistance. The MDR-TB prevalence in Malawi is at 4.8% among retreatment cases, and 0.4% among new cases (14).

### ***Antiretroviral Medicines***

The study was conducted during a transition period from the stavudine-based regimens to tenofovir-based regimens due to the side effects experienced by stavudine-based combinations (29,30). This explains the approximate 100% stock-out rate of the previous first line stavudine and lamivudine and nevirapine for both years. This was also the case for stavudine and lamivudine starter pack which was stocked out throughout 2015 and 99% of the time in 2014. Both medicine were mostly unsupplied hence the unavailability. However, stavudine first line was supplied in November 2014 and it was used by the ART clinic the same month. The new tenofovir first-line regimen was 100% available during both years.

The supply of the other new ARVs was still erratic as was shown by the first line replacement from the previous guidelines of 2011, which was abacavir 600mg and lamivudine 300mg as delivery records indicated that it was not received at the main Pharmacy. Records at the clinic however, showed that it was received as a donation from Lighthouse clinic although consumption data was unavailable. The abacavir and lamivudine combination is needed in patients with renal failure and it can also be prescribed as a non-standard first line regimen as a substitution for tenofovir and lamivudine and efavirenz, and zidovudine and lamivudine and efavirenz (30). The absence of this combination could result in renal failure patients having no treatment options or being treated with the renal toxic medicines. Studies have been conducted in Africa and they illustrated the results of stock-out of ARVs ranging from increasing the risk of HIV drug-resistant strains; treatment failure; increased risk of death; treatment interruption; increased costs for patients; and increased costs for the health systems (10,11,31–33).



### ***Antimalarial Medicines***

The results showed that there were stock-outs of antimalarial medicines in both 2014 and 2015. Quinine 300mg tablet is used in the treatment of malaria in combination with clindamycin for pregnant women, as well as in children less than 5kg (23). In 2015, it was mostly available during peak malaria season between November and April, although it was not available half of January. In 2014 quinine tablet was unavailable at some point during every month (except for January), with complete stock-outs in November, March and April. LA can be used as the second line treatment in pregnant women, and it was frequently stocked-out in both years (23). Despite the frequent LA stock-outs, the alternative ASAQ was generally available and it is recommended for second line malaria treatment. The stock cards at KCH indicated that the second line antimalarial ASAQ is barely prescribed, but prescribers opt for quinine which is meant to be reserved for intermittent preventive therapy for malaria during pregnancy (IPTP) (26). This is suggestive of bad prescribing practices that are likely to be made worse by the erratic supply of these medicines.

A systematic review systematic review of including six studies from African countries was conducted in order to assess clinicians' prescribing practices in the presence as well as in the absence of malaria medicines (34). The studies reported on prescriber practices in relation to Artemisinin Combined Therapy (ACT) stock. The review found that sometimes prescribing guidelines are not adhered to even when stock is available, however, there was some correlation between the availability of ACT and prescribing practices.

Other countries have found similar stock-outs results, and they have highlighted the disadvantages of stock-outs of these life-saving medicines. The consequences of stock-outs of antimalarial medicines in the public sector affects the patients who are unable to access treatment, or they may end up buying substandard or counterfeit medicines in the private sector (35,12). Alternatively, prescriber practices are affected by the availability of antimalarial medicines and stock-outs could encourage bad prescribing practices (34). On a more national note, man-made stock outs in public hospitals that result from theft or diversion of medicines lowers the opportunity for future funding or grants for the health systems in countries that require donor aid (36,35).

In Malawi, where antimalarial medicines are procured by donors, the possibility of the occurrence of theft in public hospitals could freeze donor aid and this would cripple the health sector which is already underfunded (15). Finally, KCH being a referral hospital serves a large population of patients who come from the whole of the central region of the country. The hospital is therefore their last resort of hope in being successfully treated. Shortages of or stock-outs of medicines may in fact be endangering their lives, not to mention the transport costs to the hospital.

### ***Limitations***

There were three main study limitations to the study data collection process. Firstly, there was some data missing and this affected the results that were found. Secondly. The data that was collected was for only one of the five referral hospitals in the country. Although they share the same supply chain systems, it cannot be concluded that the results that were found at KCH were similar to those that would be found at the other hospitals. Finally the fact that some of the study sample medicines are supplied by a parallel supply chain but were grouped with those are, may give inaccurate picture of the main supply chain system of the country.

## **Conclusions and Recommendations**

This study has shown that stock-outs of antibiotics occurred at KCH in both 2014 and 2015. There were stock-outs of medicines procured by the hospital, as well as those procured by partners through the parallel supply chain. This suggests that both parallel systems need to be improved in order to ensure that these stock-outs are minimised and avoided. The study did not assess the period prior to CMST having procurement responsibility as opposed to previous practices of hospitals being allocated part of the budget to supplement CMST procurement. Therefore it was not investigated if the change improved or worsened the supply chain for public hospitals. Currently, the supply chain system in Malawi is paper based. Therefore, whenever a stock card or register is misplaced, there is no alternative data available. This gave an incomplete picture of the medicine availability. However, 84% of the data was available and it was sufficient for valid conclusions.

In some cases alternative therapy was available, whereas in others even the alternative therapy was unavailable, meaning that patients were probably inadequately treated. In a country whereby the majority of the population relies on free healthcare, the alternative of patients seeking treatment at private facilities is not an option for most. There is a need for the Government to put in place measures that would ensure that both the main and parallel supply chain system in the country are functioning optimally, and that patients are able to access appropriate treatment and adequate health care. Secondly, prescriber practices are altered when the recommended treatment regimens are unavailable and this can cause bad prescribing practices leading to inappropriate treatment regimens for patients. Additionally, stock-outs or inadequate antimicrobials are one of the causes of AMR.

There is a need for National-level studies to investigate if these stock-outs were experienced in other public health facilities. Secondly, mixed-methods studies should be conducted in order to assess the impact of these stock-outs on the quality of health care as well as the direct consequences of these stock-outs for patients. There is also a need to introduce Antibiotic Stewardship in the public hospitals, as a national system, so that the procurement, prescribing and usage of antimicrobials is monitored and this can help reduce AMR.

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#### IV CONCLUSIONS AND RECOMMENDATIONS

This study has shown that stock-outs of antibiotics occurred at KCH in both 2014 and 2015. The stock-out periods ranged from two days to 365 days per study year. There were stock-outs of medicines procured by the hospital, as well as those procured by partners through the parallel supply chain. This suggests that both parallel systems need to be improved in order to ensure that these stock-outs are minimised and avoided. The study did not assess the period prior to CMST having procurement responsibility as opposed to previous practices of hospitals being allocated part of the budget to supplement CMST procurement. Therefore it was not investigated if the change improved or worsened the supply chain for public hospitals. Currently, the supply chain system in Malawi is paper based. Therefore, whenever a stock card or register is misplaced, there is no alternative data available. This gave an incomplete picture of the medicine availability. However, 84% of the data was available and it was sufficient for valid conclusions.

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Studies have shown that stock outs or shortages of medicines have been found in other African countries, and there is some evidence of the same in Malawi. There have been studies that have highlighted the consequences of medicines stock out or shortages, especially in malaria and HIV. The studies have outlined different angles in terms of consequences of stock outs of the medicines used to treat these conditions, ranging from pharmaco-economics to the impact on disease progression. However, the authors were unable to directly link the unavailability of HIV medicines and the outcome for patients during the study. As such, there is a need for National-level studies to investigate if essential medicines stock-outs were experienced in other public health facilities. Secondly, mixed-methods studies should be conducted in order to assess the impact of these stock-outs on the quality of health care as well as the direct consequences of these stock-outs for patients.

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